PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

FRIST: 21.9.05
VORFRISTEN: 21.7.05

To:

AKTE: NOT: U

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/013203	19.11.2004	21.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07K7/06, A61K47/48, C12N15/62

Applicant
ORTHOGEN AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Groenendijk, M Telephone No. +31 70 340-3715

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/013203

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37,39,41,44-53,55,57,59,62

because:

☒ the said international application, or the said claims Nos. 37,39,41,44-53,55,57,59,62 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-63(all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-63(all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-63
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-63
Industrial applicability (IA)	Yes:	Claims	1-36,38,40,42,54,56,58,60,61,63
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/013203

Re Item III.

1)Claims 37,39,41,44-53,55,57,59,62 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2)In response to an invitation to pay additional fees as to lack of unity (see Section IV) the applicant has not paid any fee. Consequently only subject 1 has been searched and hence can be examined.

Re Item IV.

The separate inventions are:

Inventions 1-39
Delivery peptide respectively comprising an amino acid sequence defined by SEQ ID Nos. 1-39; expression cassette as defined in claim 4, complexes as defined in claim 7 and their use as far as relating to respectively SEQ ID Nos 1-39

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The following documents are cited for the purpose of this reasoning:
D1:WO-A-02069930
D2:Mol.Cells, Vol.13, 2002, 202-208
D3:WO-A-0115511

1)Reading the claims in the light of the description the problem to be solved could initially be considered to be the provision of compounds which can be used for delivery of active agents through body membranes.
2)This problem has been solved by a plurality of solutions as defined in respectively the

independent claims 1-3. The application further relates to compositions/constructs of said compounds with active agents and their (medical) use.

3)This plurality of solutions might, a priori, be considered as satisfying the requirements of unity in which the structural features of formula I provides the special technical feature linking these different solutions.

4)However at the filing date of the application identical compounds also for use in delivery of active agents through body membranes were already known as can be illustrated by D1-D3 (actually claim 1 encompasses 39000 known compounds!):

a)D1, see particularly page 21 and example 13;

b)D2, see particularly the abstract

c)D3: see particularly Table 1, peptides 3-5,7,12,13,21.

5)In the light of these documents, the ISA considers that a common technical link based on the structural features of formula I, which could be the unifying concept, is no longer present.

6)The objective problem could therefore be considered to be the provision of alternative compounds for the use of delivery of active agents through body membranes.

7)Therefore further unified solutions should relate to (groups of) compounds sharing a common structural element which may be regarded as the special technical feature providing unity; this special technical feature should be an essential structural part common to all of the embodiments of the claimed invention (and responsible for the inventive effect), and which is absent from any solution to the same problem disclosed in the prior art.

8)Regarding all of the proposed solutions as a whole, as defined in claims 2 and 3, no common novel invariant structural features can be detected which could be considered as special technical feature providing unity to the application.

9)As no other technical features can be distinguished which, in the light of the prior art, could be considered as special technical features on which a unifying concept could be based, there is lack of unity between the plurality of claimed inventions defined in the claims of the present application (Rule 13.1 PCT). A subdivision according to structure has been made.

Only subject 1 has been searched completely.

Re Item V.

The following documents are referred to in this communication:

D1 : WO 02/069930 A (CELLGATE, INC) 12 September 2002 (2002-09-12)
D2 : Molecules and Cells, vol. 13, no. 2, 30 April 2002 (2002-04-30), pages 202-208, XP009016372 ISSN: 1016-8478

I.Novelty

In view of the available prior art the amino acid sequence SEQ ID No. 1, delivery peptides comprising it and their constructs are novel. Hence the claims 1-63 fulfil the requirements of Art.33(2) PCT.

II.Inventive step

1)The closest prior art can be considered to be represented by D1, disclosing peptides which are used for delivery of active agents through body membranes. Exemplified are, inter alia the peptides RKKRRQRRR, RKKRRQRR, RKKRRQR, KKRRQRRR AND KRRQRRR (see example 13).
2)The delivery peptides of the application are characterized by comprising an amino acid sequence KKRKKQKKRK and consequently differ structurally from said prior art.
Said peptides also exhibit the activity of transporting active agents through body membranes.
3)The problem to be solved may therefore be considered to be the provision of alternative peptides to be used as delivery peptides.
4)Having regard to the structural similarity of the present compounds to those disclosed in D1, the examiner is of the opinion that a skilled person would expect the present compounds to exhibit, at least qualitatively, the same activity as the prior art compounds. It is true that the present compounds contain a larger content of lysine residues. However D2 already disclosed that also peptides consisting entirely of lysine residues exhibit the same activity. Hence an artisan would not expect that introduction of lysine residues in the compounds of D1 would result in complete loss of activity.
Hence the present delivery peptides are considered to be merely obvious modifications of the compounds of D1, which a skilled person would be able to provide in order to solve the problem posed. Therefore inventive step can only be acknowledged if the present compounds exhibit unexpected advantageous properties. However at present said properties have not been posed nor have they become plausible otherwise.

Consequently the claims 1-3 are considered to lack inventive step under Art.33(3) PCT.

The related and/or dependent claims 4-63 do not contain features which in combination with the subject-matter of the claims they refer to would provide inventive step and therefore also are considered to contravene Art.33(3) PCT.

For the assessment of the present claims 37,39,41,44-53,55,57,59,62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.